

Special Susceptibility of the Child to Certain Radiation-induced Cancers

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The carcinogenic effects of exposure to ionizing radiation vary markedly with age, as revealed by studies of Japanese atomic bomb survivors and of Marshall Islanders exposed to fallout from U.S. nuclear weapons tests in the South Pacific in 1954. An increase in cancers of adulthood after intrauterine exposure, as reported in 1988, has not been sustained. After childhood exposure, increases in leukemia, breast cancer, and thyroid cancer are well established. The carcinogenic effects of radiation on the young have been reported after intrauterine exposures and after exposures during childhood. Cancers with short latent periods such as leukemia occur during childhood, but those with long latent periods such as breast cancer occur in adulthood. — *Environ Health Perspect* 103(Suppl 6):41–44 (1995)

Key words: radiation carcinogenesis, pediatrics, leukemogenesis, breast cancer, thyroid cancer

Intrauterine Exposures

Since 1956, Stewart and her associates (1) have published observations on cancer during childhood after a maternal history of exposure to diagnostic radiation during pregnancy [for example, Bithell and Stewart (2)]. Initially their observations were confirmed by a more objective study of obstetric records in New England by MacMahon (3). Extension of his findings, both geographically and in time, still showed a 1.5-fold excess of childhood leukemia, but no longer showed any increase in the relative risk of other childhood cancers (4). Other studies also failed to show any increase, notably among the Japanese atomic bomb survivors exposed *in utero* (5). In 1985, in an editorial in the *New England Journal of Medicine* (6), MacMahon wrote, "It seems likely that the question of the association between fetal irradiation and childhood cancer will fade into medical history unresolved and remain a source of more confusion than enlightenment."

An excess of cancer among the Japanese exposed *in utero* has been reported in a

study through 38 years of age (until 1984) (7). The cancers are listed in Table 1, and a dose-response effect is shown in Figure 1. The authors concluded that further follow-up is needed, but the results to date suggest "that susceptibility to radiation-induced cancers is higher in pre- than in postnatally exposed . . . adults." It should be noted, however, that the cancers in the several dose categories show no greater frequency of types known to be induced by radiation in the heavily exposed as compared with the lightly exposed or nonexposed. Of the six cancers observed at 0.30+ Gy (gray, unit of absorbed dose of ionizing radiation), three are not known to be induced by radiation

exposure: histiocytosis, liver cancer, and Wilms' tumor. Of the seven cancers in the 0.01 to 0.29 Gy dose category, only choriocarcinoma has not been linked to radiation exposure. In this group, there is as yet no breast cancer, the solid tumor most easily induced by radiation. In the nonexposed, three of the five cancers were breast cancers and the other two were uterine cancer, which has not been related to radiation exposure. The group with intermediate exposures (0.01–0.29 Gy) had the highest proportion of cancers known to be radiogenic. From this perspective, the distribution of diagnoses by exposure category does not yet reveal a dose-response effect.

Table 1. Cancer among Japanese exposed *in utero* to the atomic bomb.^a

Dose ^b	Cancer	Age <i>in utero</i> , weeks	Age at onset, year	Radiogenic ^c	% Radiogenic
2.13	Ovary	36	22	+	3/6 = 50%
1.39	Liver	8	6 ^d	+	
0.90	Stomach	17	29	+	
0.58	Histiocytosis	36	35	+	
0.56	Wilms' tumor	15	14	+	
0.40	Thyroid	22	34	+	6/7 = 86%
0.21	Stomach	3	24	+	
0.08	Colon	7	21 ^d	+	
0.04	Leukemia	4	29	+	
0.02	Leukemia	38	18	+	
0.01	Choriocarcinoma	36	34	+	
0.01	Bladder	23	22	+	
0.01	Stomach	32	35	+	3/5 = 60%
0	Breast	34	29	+	
0	Breast	26	38	+	
0	Breast	3	32	+	
0	Uterus	17	34	+	
0	Uterus	8	34 ^d	+	

^aFrom Yoshimoto et al. (7). ^bDose is measured in gray (Gy), a unit of absorbed dose of ionizing radiation. ^cKnown to be inducible by ionizing radiation. ^dAge at death.

This paper was presented at the Symposium on Preventing Child Exposures to Environmental Hazards: Research and Policy Issues held 18–19 March 1994 in Washington, DC. Manuscript received: December 5, 1994; accepted: May 15, 1995.

This article is extracted and updated from DP Merke and RW Miller. Age differences in the effects of ionizing radiation. In: *Similarities and Differences between Children and Adults. Implications for Risk Assessment* (Guzelian PS, Henry CJ, Olin SS, eds). Washington:ILSI Press, 1992;139–149.

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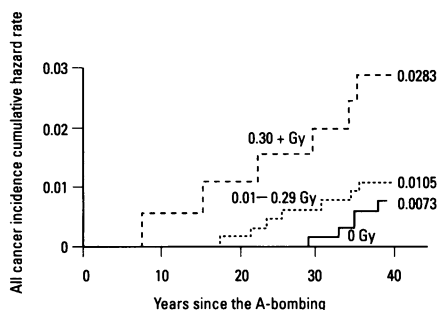


Figure 1. Cumulative hazard rate for cancer among survivors of intrauterine radiation in Hiroshima and Nagasaki through 1984 for three exposure groups. From Yoshimoto et al. (7).

In the 5 years that have passed since Yoshimoto et al. (7) published their report, the excess has not been sustained (8). The fetus should be susceptible to radiation carcinogenesis, and an excess of radiogenic cancers may well occur in the next few years as cancer rates rise with further aging. It is difficult to see, however, why exposure to ionizing radiation late in gestation should be more carcinogenic than exposure in early childhood.

Childhood Exposures

Leukemia

The relationship of leukemia occurrence to age of exposure to ionizing radiation has been well demonstrated (Figure 2) (5). Among survivors exposed at under 15 years of age, the peak occurred 5 years after exposure and was sharp. The leukemogenic effect disappeared at about 23 years after exposure. In successively older cohorts, the effect occurred later and the peak flattened.

The distribution of cases by cell type, from 1950 to 1978, is shown in Table 2. Although the numbers are small, it can be

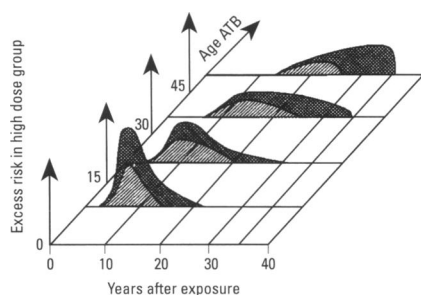


Figure 2. Diagram of the leukemia frequency among atomic bomb survivors by age at exposure, latent period, and city (Hiroshima, black; Nagasaki hatched). ATB, at time of bomb. From Ichimaru et al. (5).

Table 2. Annual incidence rates per 100,000 of leukemia by cell type^a among survivors who received 1 Gy or more, by age at exposure.

	Age at the time of the bomb			
	<15	15-29	30-44	45+
Person-years	41,326	54,559	32,205	19,011
Cell type	Annual incidence rates (n)			
CML	14.5 (6)	7.3 (4)	15.5 (5)	5.3 (1)
AML	2.5 (1)	12.8 (7)	27.9 (9)	36.8 (7)
ALL	12.1 (5)	9.2 (5)	6.2 (2)	5.3 (1)
AL	12.1 (5)	9.2 (5)	6.2 (2)	5.3 (1)

Abbreviations: CML, chronic myelogenous leukemia; AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; AL, acute leukemia, not otherwise specified or of other types. ^aFrom Ichimaru et al. (5).

seen that chronic myelogenous leukemia (CML) occurred in children, among whom it is usually rare, as well as among adults. Acute myelogenous leukemia (AML) was rare when exposure was under age 15 at the time of the bomb (ATB); acute lymphocytic leukemia (ALL) was rare among those who were over 30 years old ATB. Thus, the type of leukemia induced by radiation was related to age at exposure, and, except for CML, followed the distribution of leukemia by cell type in nonirradiated populations. A more accurate evaluation has been made through a reanalysis of leukemia cases through 1980 using the French-American-British classification method and the most recent revision in dosimetry (DS-86), but the interpretation of the age effect on cell type has not changed (9).

Breast Cancer

Among atomic bomb survivors exposed to 1+ Gy, age ATB has been found to be a strong influence on the risk of breast cancer (10) (Figure 3). Risk was greatest among those under 15 years ATB and fell there-

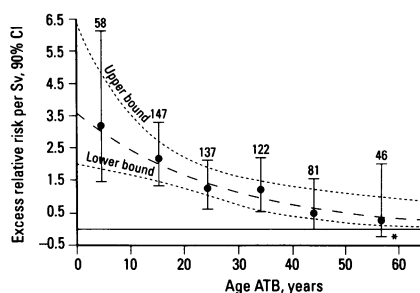


Figure 3. Relative risk of breast cancer by age at exposure to 1 or more Gy. From Tokunaga et al. (10). *Minimum feasible value for lower limit. ATB, age at the time of the bomb.

after until 39 years of age. Only a small increase occurred after age 40. The latent period was at least 10 years, and the increase did not occur before age 30, i.e., the usual age for developing breast cancer. By contrast, the risk of leukemia increases within a few years after exposure regardless of age ATB.

Thyroid Cancer

Studies of human populations exposed to radioisotopes of iodine have not shown an increase in the frequency of thyroid cancer except in the Marshall Islands. There, the population was exposed to both internal and external irradiation fallout from a nuclear weapons test in 1954. The internal dose was mostly from short-lived I 133 and I 135, and only about 10 to 20% came from I 131 (11). Exposures elsewhere, as at Chernobyl, were originally thought to be mainly due to I 131, which, at its lower dose rate, is far less damaging. An unpublished report of about 200 cases of childhood thyroid cancer in Belarus since the accident may signal that other radioiodines were involved.

The heaviest exposure to I 131 was in the Marshall Islands in 1954, where fallout from a nuclear weapons test occurred. Sixty-four people on the island of Rongelap received 10 to 50 Gy to the thyroid from radioiodines, plus 1.9 Gy whole-body exposure from external radiation. The 18 people on Ailingnae received up to 13 Gy to the thyroid, plus 1.1 Gy of external radiation. On Uterik 159 people received up to 6.7 Gy to the thyroid and 0.11 Gy from external radiation (11,12). These doses were far greater than those in Ukraine and Belarus.

Two of the nine children exposed on Rongelap at 1 year of age, when the thyroid was small and its activity was great, developed myxedema and short stature (Table 3). The remaining seven developed thyroid nodules. Although hypofunction occurred in people who were older when exposed, none were of the severity observed in the two who were exposed at 1 year of age (13). The proportion with nodules diminished with age at exposure, and only one person exposed at over 10 years of age was affected. Carcinoma developed in five of 24 persons exposed at 5 to 29 years of age. In all of the people exposed on Rongelap, 21 of 54 developed these disorders. Figure 4 shows the difference in the frequency of nodules or cancer among those on Rongelap or Ailingnae under 10 years of age compared with those who were older at exposure.

Table 3. Thyroid disorders after exposure in 1954 on Rongelap among those who survived at least until 1964.^a

Age ^b	Dose, ^c Gy	Number	Myxedema	Nodules	Carcinoma
1	50	9	2	7	0
2	30-40	5	0	3	0
5-9	20-28	6	0	3	1
10-19	11-18	12	0	0	3
20-29	10-11	6	0	1	1
30+	10	16	0	0	0
Total		54	2	14	5

^aFrom Adams et al. (12). ^bAt exposure. ^cDue to radioiodines; in addition, each person received 1.9 Gy from external radiation.

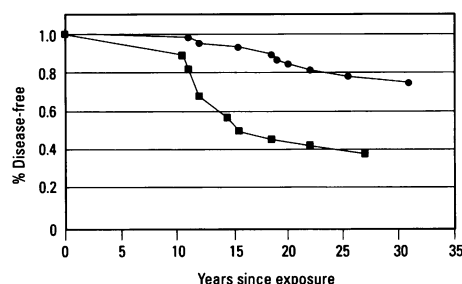


Figure 4. Development of thyroid nodules or carcinoma among Marshallese exposed on Rongelap or Ailingnae, exposure under age 15 compared with 15+. Data from Lessard et al. (11). (■), Age < 10 at exposure ($n=28$); (●), age > 10 at exposure ($n=54$). $p<0.001$.

Thyroid nodules and carcinoma were not diagnosed until 10 years after exposure, which implies a latent period of this duration regardless of age at exposure. This latent period is the time from exposure to clinical detection; the latent period between exposure and thyroid dysfunction may be shorter (11).

From these data, it is clear that exposure to fallout from a nuclear weapons test caused effects on the thyroid that were frequent, severe, and age-related. The dose estimates, based on age, indicate an increased uptake of iodine by smaller thyroid glands, resulting in larger doses among the young.

Research Needs

There are two main needs. The data from those exposed to the atomic bombs in Japan *in utero* or during childhood have provided the best data available on carcino-

genic effects from external radiation exposure. This information, over a wide spectrum of doses, is the basis for national and international standards for radiation protection. The children who were *in utero* or under 10 years of age ATB will be 50 to 60 years old in 1995. Cancer rates mount rapidly with each passing year. The collection of incidence data on cancer, far more reliable than death-certificate data, is about to reveal the full magnitude and the mechanisms of radiation carcinogenesis in the most cancer-prone age range. The United States and Japan provide equal funding for these studies. Data collection is in peril due to impending deep U.S. budget cuts. Influential persons in and out of government must be enlisted to prevent the collapse of these studies.

The second need is for the training of a few pediatricians in the late effects of ionizing radiation. Those who were trained in about 1950 are reaching the end of their careers and, with regard to experts on pediatric exposures, there are no replacements in sight. An intimate knowledge of pediatric cancer and of radiation effects is required. The obvious place to look is in academic pediatrics, possibly pediatric radiology, where a few young physicians might focus on radiation effects in addition to their principal interest. The training could be sponsored by a foundation or government agency as it was in 1950.

Conclusions

Ample data are available for studies of age differences in radiation effects, based on external exposures among Japanese atomic-

bomb survivors and high thyroid doses among Marshallese exposed to fallout. The increase in cancer occurrence reported among the *in utero*-exposed group is still tentative. As yet, these individuals show no evidence that their risk of cancer is greater than that of persons who were older when exposed. There is, however, clear evidence that susceptibility to certain cancers is greater among those with childhood exposure than among those exposed later in life. Susceptibility to leukemia was greater and the cell-type distribution was different among those under 20 years of age than among persons who were older ATB. The peak leukemia incidence occurred 5 years after exposure. Age-related host susceptibility apparently affects the frequency and type of leukemia induced by radiation.

The risk of breast cancer also is highest among those exposed under 20 years of age. Only a small increase was observed among those who were exposed at 40+ years of age. Breast cancer did not develop among persons exposed as children or adolescents until they reached the usual age for breast cancer, in contrast to leukemia, for which the latent period at all ages is similar. Breast cancer requires aging and is apparently related to hormone status at exposure and when the neoplasm develops.

Benign thyroid neoplasia from radioiodine fallout on the Marshall Islands was related to the rate of iodine uptake by the thyroid, which is greatest early in life. Thus, age is correlated with dose. The excessive occurrence of thyroid carcinoma among those exposed at 5 to 29 years of age indicates that something in addition to dose influences malignant transformation.

Radiation effects have been studied over a wide range of age and dose, more so than other environmental exposures. The marked influence of age on the frequency of radiation effects is related to fetal or postnatal development. The diversity of the age relationships indicates that a variety of mechanisms is involved.

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